Canadian Journal of Cardiology 35 (2019) 185–192

Clinical Research

Clinical Utility of Pre-Exercise Stress Testing in People With Diabetes

Marni J. Armstrong, PhD,[a] Doreen M. Rabi, MD, MSc,[b,c,d,e] Danielle A. Southern, MSc,[f] Alykhan Nanji, MD, MPH, MBA,[g] William A. Ghali, MD, MPH,[b,c,e] and Ronald J. Sigal, MD, MPH[b,c,d,e,f]

[a] *Department of Cardiovascular & Respiratory Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[b] *Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[c] *Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[d] *Department of Cardiac Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[e] *O'Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada*
[f] *Faculty of Kinesiology, University of Calgary, Calgary, Alberta, Canada*
[g] *C-era Medical Clinic, Calgary, Alberta, Canada*

See editorial by Banks and Connelly, pages 150–152 of this issue.

ABSTRACT

Background: Although suggested by practice guidelines, the need for pre-exercise stress testing in asymptomatic people with diabetes remains controversial. We examined the utility of screening with pre-exercise stress testing in patients with diabetes.

Methods: We completed a cohort study, evaluating patients with diabetes who attended an exercise program intake session between 2007 and 2012. The exposure of interest was referral for pre-exercise stress testing determined by an algorithm requiring sedentary patients with diabetes and $\geq$ 1 cardiac risk factor to undergo testing. Outcomes included cardiac catheterization, revascularization, cardiovascular-related admissions, mortality, and change in care.

Results: Among 1705 people with diabetes, 676 (40%) were referred for pre-exercise stress testing. In patients who were referred for stress testing compared with those who were not, there was no difference in the composite of cardiovascular outcomes (revascularization, cardiovascular-related admissions, and cardiovascular-related death)

RÉSUMÉ

Introduction : Bien que les lignes directrices suggèrent de faire passer l'épreuve d'effort chez les personnes asymptomatiques atteintes du diabète avant d'entreprendre une activité physique, cette pratique demeure controversée. Nous avons examiné l'utilité du dépistage au moyen de l'épreuve d'effort chez les patients diabétiques avant d'entreprendre une activité physique.

Méthodes : Nous avons terminé une étude de cohorte, qui portait sur l'évaluation de patients diabétiques qui avaient participé à une séance d'admission au programme d'activité physique entre 2007 et 2012. L'exposition d'intérêt était la consultation pour l'épreuve d'effort avant d'entreprendre une activité physique déterminée par un algorithme qui requiert des patients sédentaires atteints du diabète et ayant $\geq$ 1 facteur de risque cardiaque pour subir l'épreuve. Les critères de jugement étaient le cathétérisme cardiaque, la revascularisation, les admissions liées aux maladies cardiovasculaires, la mortalité et les changements dans les soins.

People with diabetes are at increased risk of cardiovascular disease (CVD),[1-4] and habitual exercise is associated with substantial reduction of this risk.[5-9] However, acute exertion can also precipitate coronary events.[10,11] Because of the higher prevalence of silent ischemia in diabetes, several practice guidelines[12-14] suggest that exercise stress testing be considered for the majority of asymptomatic diabetic persons who want to perform moderate to vigorous exercise training and/or who have other CVD risk factors. Although the updated guidelines[12] from the American College of Sports Medicine (ACSM) no longer recommend screening based on traditional CVD risk factors for the general population, the recommendation for inactive people with diabetes is to obtain "medical clearance" before participation in even moderate-intensity exercise. The guidelines further state that for people with diabetes and a risk of a cardiac event over 10 years of > 10% using the Framingham Risk Calculator,

Received for publication June 14, 2018. Accepted November 14, 2018.

Corresponding author: Dr Marni J. Armstrong, Diabetes Clinical Trials Unit, 1820 Richmond Road SW, Calgary, Alberta T2T 5C7, Canada. Tel.: +1-403-955-8119.
E-mail: marni.armstrong@gmail.com

See page 191 for disclosure information.

https://doi.org/10.1016/j.cjca.2018.11.007

within 1 year (2.8% vs 1.9%, $P = 0.250$), or subsequent to the first year (3.1% vs 4.6%, $P = 0.164$). Within 1 year, more revascularizations were performed in patients referred for stress testing compared with those who were not (2.1% vs 0.8%, $P = 0.027$) but not during longer-term follow-up (mean 3.4 years).

Conclusions: The rates of cardiovascular outcomes in both tested and untested patients were low. Patients undergoing stress testing had no difference in adverse cardiovascular outcomes over the follow-up periods. Referral for stress testing did not result in a change in care for most patients. Our findings suggest stress testing before beginning an exercise program is not necessary for most asymptomatic patients with diabetes.

Résultats : Parmi les 1705 personnes diabétiques, 676 (40 %) ont subi l'épreuve d'effort avant d'entreprendre une activité physique. Si l'on comparait les patients qui passaient l'épreuve d'effort à ceux qui ne le passaient pas, il n'y avait aucune différence dans les critères composites des événements cardiovasculaires (revascularisation, admissions liées aux maladies cardiovasculaires et décès liés aux maladies cardiovasculaires) en 1 année (2,8 % *vs* 1,9 %, $P = 0,250$), ou après la première année (3,1 % *vs* 4,6 %, $P = 0,164$). En 1 année, mais non au cours du suivi à long terme (moyenne de 3,4 ans), les patients qui passaient l'épreuve d'effort subissaient plus de revascularisations que ceux qui ne la passaient pas (2,1 % *vs* 0,8 %, $P = 0,027$).

Conclusions : Les taux d'événements cardiovasculaires chez les patients qui subissaient l'épreuve d'effort et les patients qui ne subissaient pas l'épreuve d'effort étaient faibles. Les patients qui subissaient l'épreuve d'effort ne montraient aucune différence dans les événements cardiovasculaires indésirables durant les périodes de suivi. La consultation pour l'épreuve d'effort n'entraînait pas de changement dans les soins de la plupart des patients. Nos résultats montrent que la plupart des patients diabétiques asymptomatiques n'ont pas besoin de passer l'épreuve d'effort avant de commencer un programme d'activité physique.

or participating in vigourous-intensity exercise, that an exercise stress test be considered before exercise. Although stress testing can be useful for determining functional capacity and guiding exercise prescription,[13,15] the value and clinical utility of pre-exercise stress testing to screen for CVD in patients with diabetes is uncertain.[16]

Several trials investigating screening for CAD in asymptomatic patients with type 2 diabetes found that screening with coronary computed tomography angiography,[17] myocardial perfusion imaging,[18] or electrocardiography (ECG) stress testing[19] did not reduce rates of cardiac events in follow-up. Accordingly, recent guidelines[20,21] do not recommend routine CAD screening in all people with diabetes. However, this evidence does not necessarily apply to those who wish to initiate exercise, for whom stress testing remains recommended for many.[12-14] With an increasing number of public health efforts to promote physical activity in people with diabetes, the decision to refer for pre-exercise stress testing is encountered frequently by many health care providers.

The aim of this study was to evaluate the clinical utility of pre-exercise stress testing in people with diabetes planning to enter a supervised exercise program within a community-based cohort. Specifically, we evaluated differences in cardiovascular outcomes among those who were referred, vs not referred, for pre-exercise stress testing. Our secondary objectives were to compare the clinical characteristics of patients referred for pre-exercise testing who experienced a CV outcome with those who did not, to determine clinical predictors of CV events and to determine if referral for stress testing led to a change in care.

Methods

Inception of cohort

We conducted a retrospective cohort study of patients referred to a supervised exercise program between March 1, 2007 and February 29, 2012, in Calgary, Alberta, Canada. Patients were included if they were at least 18 years of age, attended an exercise intake session, and were identified as having "diabetes mellitus" or "type 2 diabetes." The supervised exercise program or the "Living Well" program is a community-based 8-week, medically supervised exercise program. Participants were self-referred or referred by health care providers. All participants were required to attend an orientation/intake session during which they were given information, triaged to the appropriate level of class, and screened by clinical staff using an algorithm to determine if a stress test was necessary before the exercise program. The Alberta Health Services Chronic Disease Management (CDM) Database captures Living Well program data including sex, age, and current medical conditions. The CDM database was used to identify patients with diabetes who attended the exercise intake session and ascertain if they were triaged for a pre-exercise stress test.

Key exposure of interest

Referral for pre-exercise stress testing was the exposure of interest. The pre-exercise stress testing algorithm required patients with diabetes who were sedentary and had ≥ 1 other cardiac risk factor, or reported symptoms suggesting angina, to undergo stress testing prior to the exercise program. The algorithm was put in place to be consistent with existing guidelines; however, it did not advise testing every middle-aged person with diabetes as was suggested by guidelines at the time.[14,22] To obtain the testing details and clinical information of those attending the screening visit, chart reviews at cardiovascular screening clinics were performed. Data on presence or absence of prespecified clinical characteristics and comorbidities, type(s) of testing performed, outcomes of the testing, whether or not the patient was ultimately cleared for the exercise program, and whether or not the referral to pre-exercise screening resulted in a change in care were systematically abstracted from patient charts. A "change in care" was defined as any change that happened as a result of the screening visits that would otherwise not have occurred through routine clinical care. The exercise stress tests were conducted at 3 community cardiovascular screening clinics. In most cases (98%), the Bruce treadmill protocol[23] was used with a small number (2%) completed using the modified Bruce protocol.[24] Upon presentation at the cardiovascular screening clinics, a number of patients (n = 38, 7.3%) were referred directly to nuclear testing owing to perceived unsuitability for a treadmill test, usually due to pain, low mobility, extreme obesity, or symptoms of angina or severe shortness of breath on minor exertion.

Outcomes of interest

Cardiac catheterization, revascularization procedures, CVD-related hospital admissions, all-cause mortality, and cardiovascular (CV) mortality were the CV outcomes assessed. Follow-up was complete by December 31, 2012 for all patients. Data from administrative and clinical databases were linked on a unique identifier. The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease[25] database was used to obtain detailed clinical information on all adults undergoing cardiac catheterization and revascularization in Alberta. The hospital administrative inpatient Discharge Abstract Database was used to obtain data on all cases experiencing a cardiovascular hospital admission. Cardiac-specific hospitalizations for acute coronary syndrome and stroke were determined by the use of International Classification of Diseases, (ICD-10) codes.[26,27] The diagnostic codes for myocardial infarction (MI) (I21.X, I22.X), unstable angina (I20.X, I24.X), stroke (I63.X, I64.X), transient ischemic attack (G45.X), bleeding (I60.X, I61.X) and venous sinus thrombosis (I63.6, I67.7, G08.X) were employed. All admissions were categorized according to the main discharge diagnosis and coded as "cardiovascular-related" or not. Provincial Vital Statistics data were used to determine date of death and cause of death. All-cause mortality was considered as well as CV-related deaths. We examined outcomes within 1 year, after 1 year, and over the entire follow-up period (2007 to 2012). We considered CV death and admission for acute MI (AMI) as major adverse CV events. We also considered a composite of CV outcomes defined as any of revascularization procedures or CV-related admission or CV-related death. The study was reviewed and approved by the University of Calgary Research Ethics Board.

Statistical analysis

Baseline age and sex were compared between patients identified as requiring referral for screening vs those who were not. Differences in categorical data were assessed using χ^2 tests, and differences in continuous data were assessed using Students' *t*-tests. Differences in outcomes within 1 year of the exercise intake session, after the intake session, and over the entire study period were examined according to the requirement for a pre-exercise stress test referral. Categorical variables are presented as frequencies and percentages, and continuous variables as mean (SD) values. Because of the small number of cases, differences in categorical data were assessed using Fisher's exact test. Logistic regression analysis was used to assess odds ratios, and the models were adjusted for age and sex. All statistical tests with 2-sided P value ≤ 0.05 were considered significant.

Results

A total of 1705 participants with diabetes who attended an exercise intake session over the study period were identified. Among these, 676 (40%) required referral for pre-exercise stress testing according to the Living Well program's algorithm for stress testing referrals. Figure 1 demonstrates the flow and derivation of the study cohort. Participants (n = 32) considered more appropriate for a cardiac rehabilitation program (eg, with a recent MI or revascularization procedure) were referred directly to that program and excluded from this analysis. Participants (n = 336) of low physical functioning (incapable of achieving at least 3 metabolic equivalents) and triaged to the low function exercise class were also excluded. Baseline characteristics are displayed in Table 1. Mean age of the cohort was 60.2 years, and 41% were male patients, with no differences between those referred vs not referred for stress testing. Age and sex from the CDM database were available on the entire cohort; all other variables were extracted by chart review therefore only available on those referred for stress testing and those experiencing a CV outcome.

Table 2 compares CV outcomes in participants referred for pre-exercise stress testing to those not requiring a stress test. The mean (SD) follow-up time was 3.4 (1.4) years. Within 1 year of intake—and over the entire follow-up period—there were no significant intergroup differences in any of the CV event outcomes or the composite of CV outcomes. In patients who were referred for stress testing compared with those who were not, there was no difference in the composite of cardiovascular outcomes within 1 year (2.8% vs 1.9%, $P = 0.250$), or after the first year (3.1% vs 4.6%, $P = 0.164$). For interventional outcomes, within only the first year there were significantly more catheterization procedures in patients who were referred for pre-exercise stress testing (4.3% vs 2.2%, $P = 0.021$), as well as more revascularization procedures (2.1% vs 0.8%, $P = 0.027$). Corresponding unadjusted and adjusted odds ratios (95% confidence interval) for patients undergoing stress testing relative to those not tested were not significant for the composite of any CV outcome, whereas the corresponding odds ratios indicating higher use of catheterization and revascularization were statistically significant (Supplemental Table S1). It should be noted that, in the referral group, only 38% of the catheterizations and 20% of the revascularizations performed were identified as being a direct result of the referral for pre-exercise stress testing. The differences were not significant between the groups after the first year and over the entire follow-up period. The rate for major adverse CV events (CV death and AMI) was very low. Within the first year, the event rates were 0.7% in both groups, with an average rate of 0.88% and 0.82% over the mean follow-up period in the nonreferred and the referred group, respectively.

Table 3 outlines the age and sex characteristics of patients experiencing CV outcomes within 1 year of the exercise intake. Patients who were male and older were significantly more likely to experience an outcome. Details of other clinical characteristics were not available on the entire cohort.

Among patients referred for pre-exercise stress tests, chart review data were available on 524 patients. Table 4 outlines the proportions of patients who were identified with risk factors in

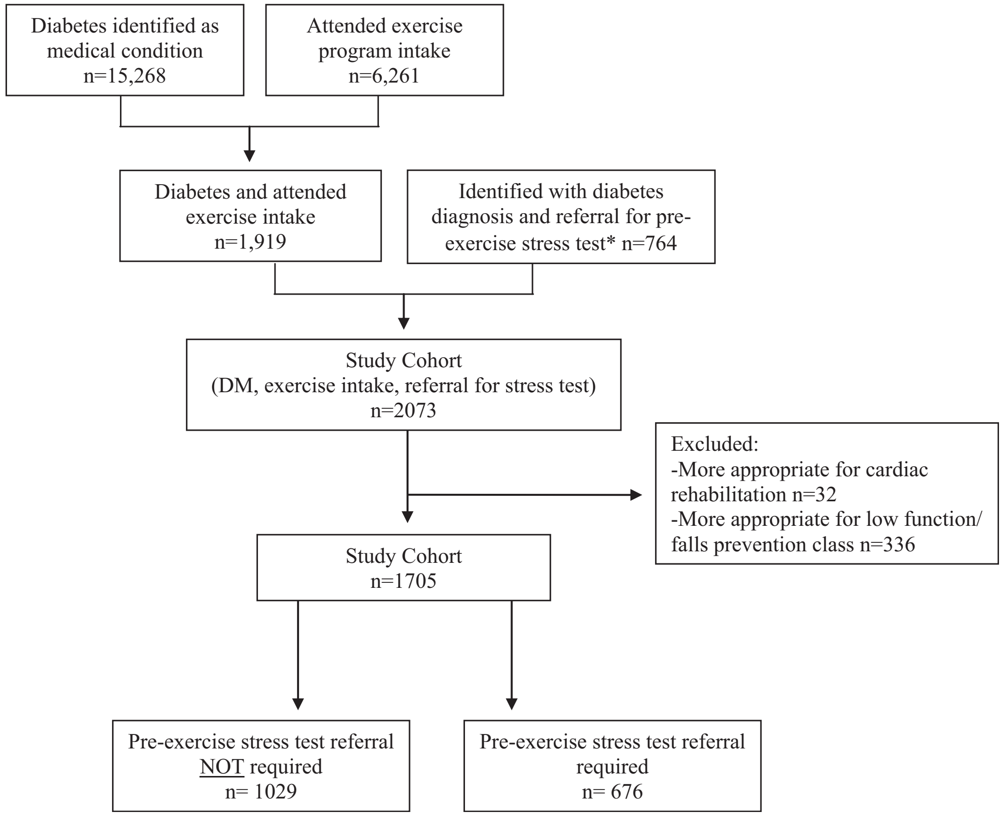

Figure 1. Derivation of study population flow diagram. Referral for stress test required if patient has a diagnosis of diabetes, previously sedentary, and ≥ 1 other cardiovascular risk factor. *Data obtained from screening clinics chart reviews.

the chart review, stratified by whether or not they experienced a CV outcome. Patients who experienced CV outcomes were significantly older, more frequently male, and more likely to have had previous MIs or stroke, previous cardiac arrhythmias, and/or diagnoses of congestive heart failure (CHF), compared with those who did not experience an outcome. Patients with CV outcomes also had nonsignificantly higher rates of diabetic neuropathy, nephropathy, and/or retinopathy than those who did not experience CV outcomes. Moreover, those patients who experienced outcomes were more likely to have experienced chest pain upon testing at the screening clinics. Among the patients (n = 39) who experienced CV outcomes within 1 year of intake, all had at least 1 of the following risk factors at baseline: symptoms of chest pain, previous CV event, previous arrhythmia, severe chronic obstructive pulmonary disease (COPD), diabetes-related nephropathy or neuropathy, and/or age over 80 years. It should be noted that 65% of all those referred for stress testing did not have any of these risk factors. Notably, of the 19 patients who experienced CV outcomes within 1 year of intake and had referrals for stress testing, 6 (32%) of the CV outcomes occurred *after* these patients had been cleared for the exercise program (4 = percutaneous cardiology intervention [PCI], 1 = MI, 1 = death).

Chart reviews revealed that 10.3% of patients did not attend the screening visits. It also revealed that, in 14% of the cases (n = 73), the screening referral indicated patient-reported chest pain/ischemia-related symptoms. Available baseline ECGs revealed that 50% of patients were reported to have "normal" baseline ECGs, whereas another 21% had the baseline ECG listed as "other," which included nonspecific or minor ST-changes or a minor heart block such at right bundle branch block or first-degree atrioventricular (AV) block and

Table 1. Baseline characteristics of patients with diabetes attending exercise intake session

	Whole cohort	Referral for stress test NOT required*	Referral for stress test required*	*P* value (no stress test vs stress test)
Sample size (n)	1705	1029	676	
Mean age, years (SD)	60.2 (11.3)	60.1 (11.3)	60.4 (11.3)	0.5110
Percent male, n (%)	705 (41.4%)	415 (40.3%)	290 (42.9%)	0.292

Age and sex are only available variables from database; all other variables had to be extracted by chart review.

SD, standard deviation.

* Referral for stress test required if previously sedentary and ≥ 1 other cardiovascular risk factor (obesity, body mass index > 30; hypertension; dyslipidemia; smoking, current or quit within previous 6 months; family history; major adverse cardiovascular event before 55 years in father or other male first-degree relative or before 65 years in mother or other first-degree relative).

Table 2. Cardiovascular outcomes by pre-exercise stress testing referral status

	Within 1 year of exercise intake			After first year			Entire follow-up period (2007 to 2012)		
	Referral for stress test NOT required n = 1029	Referral for stress test required n = 676	*P* value	Referral for stress test NOT required n = 1029	Referral for stress test required n = 67	*P* value	Referral for stress test NOT required n = 1029	Referral for stress test required n = 676	*P* value
CATH procedures									
Total	23 (2.2%)	29 (4.3%)	**0.021**	43 (4.2%)	27 (4.0%)	0.901	66 (6.4%)	56 (8.3%)	0.115
Result of referral*		11 (1.6%)							
Revascularization									
Total	8 (0.8%)	14 (2.1%)	**0.027**	21 (2.0%)	11 (1.6%)	0.589	29 (2.8%)	25 (3.7%)	0.325
Result of referral*		3 (0.4%)							
PCI									
Total	4 (0.4%)	9 (1.3%)	**0.043**	12 (1.2%)	8 (1.2%)	1.0	16 (1.6%)	17 (2.5%)	0.208
Result of referral*		3 (0.4%)							
CABG									
Total	4 (0.4%)	5 (0.7%)	0.332	10 (1.0%)	3 (0.4%)	0.266	14 (1.4%)	8 (1.2%)	0.829
Result of referral*		0							
CV admission	14 (1.4%)	11 (1.6%)	0.684	21 (2.0%)	14 (2.1%)	1.0	35 (3.4%)	25 (3.7%)	0.789
Major adverse CV events	7 (0.7%)	5 (0.7%)	1.0	24 (2.3%)	14 (2.1%)	0.867	31 (3.0%)	19 (2.8%)	0.883
MI admission	3 (0.3%)	3 (0.4%)	0.687	7 (0.7%)	7 (1.0%)	0.426	10 (1.0%)	10 (1.5%)	0.364
CV death	4 (0.4%)	2 (0.3%)	1.0	17 (1.7%)	7 (1.0%)	0.401	21 (2.0%)	9 (1.3%)	0.348
Non-CV death	12 (1.2%)	5 (0.7%)	0.462	24 (2.3%)	14 (2.1%)	0.867	36 (3.5%)	19 (2.8%)	0.485
All-cause death	16 (1.6%)	7 (1.0%)	0.400	41 (4.0%)	21 (3.1%)	0.359	57 (5.5%)	28 (4.1%)	0.212
Any CV outcome†	20 (1.9%)	19 (2.8%)	0.250	47 (4.6%)	21 (3.1%)	0.164	67 (6.5%)	40 (5.9%)	0.683

P values are determined by Fisher's exact test. Bold values represent statistically significant values.

CABG, coronary artery bypass graft; CATH, catheterization; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention.

* Outcome occurred as direct result of referral for pre-exercise stress test.

† Any CV outcome is defined as 1 or any of the following: CV death, revascularization procedure (PCI or CABG), or CV admission.

Table 3. Age and sex of patients experiencing CV outcome within 1 year

	No stress test referral			Stress test referral		
	No CV outcome	CV outcome	*P* value	No CV outcome	CV outcome	*P* value
Sample size (n)	1009	20		657	19	
Mean age, years (SD)	59.9 (11.3)	68.6 (9.4)	**0.0006**	60.2 (11.2)	68.4 (8.5)	**0.0017**
Male sex, n (%)	403 (40.0%)	12 (60%)	0.070	275 (41.9%)	15 (79.0%)	**0.001**

CV outcome is defined as one of CV death, revascularization (percutaneous coronary intervention or coronary artery bypass graft), CV admission within 1 year of exercise intake session. *P* value is for comparison between no CV outcome vs CV outcome. Bold values represent statistically significant values.

CV, cardiovascular; SD, standard deviation.

other less common abnormalities (see Supplemental Tables S2 and S3 for further details). Among all patients (n = 441) who completed stress tests, mean (SD) exercise capacity was 6.8 (2.3) metabolic equivalents. Among those reporting no chest pain/symptoms who completed stress tests, 69% were cleared for the exercise program, whereas in those patients reporting chest pain, 50% were cleared. The remainder were identified as requiring further testing (mostly nuclear) before clearance for the exercise program. Ultimately, 19 patients (3.6% of 524) were not cleared for exercise upon nuclear testing; 11 were considered candidates for cardiac catheterization; 1 patient refused nuclear testing; 1 patient did not show for follow-up after nuclear testing; and the remainder were deemed more appropriate for the local cardiac rehabilitation program, which included more cardiac monitoring and aggressive risk-factor modification (see Supplemental Table S4 for details on nuclear testing). Among those referred for cardiac catheterization, 3 had PCI interventions, 6 had false positive myocardial perfusion imaging (MPI) results, 1 had identified collateral circulation and no intervention, and 1 was admitted with ST-elevated MI (STEMI) while waiting and had an urgent PCI. Among patients referred for stress testing whose charts were reviewed, only 4.6% were identified as undergoing a change in care as a result of the stress-testing referral. The most common change in care was that the patient was deemed more appropriate for a cardiac rehabilitation program, followed by the discovery of a previously unidentified cardiac arrhythmia.

Discussion

In this community-based cohort of people with diabetes initiating an exercise program, we found that the rate of CV outcomes was very low. Referral for stress testing was not associated with an improvement in CV outcomes over follow-up and was associated with a change in care in only a small proportion of patients. Within the first year of intake, referral for pre-exercise stress testing was associated with higher rates of revascularization, although the absolute rates of intervention were extremely low (n = 3, 0.4%).

Although recommended by practice guidelines,[12-14] our findings suggest that pre-exercise stress testing in asymptomatic middle-aged diabetic patients is of limited utility for screening for safety. The guidelines suggesting stress testing for most people with diabetes are not substantiated by strong evidence, and our findings suggest that they should be reconsidered. More appropriate risk stratification should be rigourously applied, as our study found that patients who experienced events were more likely to have had previous CV events, previous arrhythmias, CHF, and/or known diabetic microvascular complications. Not surprisingly, symptoms of chest pain were also associated with increased rates of CV

Table 4. Risk factors in patients referred for pre-exercise stress testing: comparison between those with and without CV outcome

Risk factor	Overall n = 524	No CV outcome n = 505	CV outcome n = 19	*P* value*	Odds ratio (95% CI)	Adjusted† OR (95% CI)
Male sex, n (%)	223 (42.6%)	208 (41.2%)	15 (80.0%)	**0.001**	5.35 (1.75, 16.36)	4.59 (1.49, 14.15)
≥ 60 years old, n (%)	284 (54.2%)	268 (53.1%)	16 (84.2%)	**0.009**	4.72 (1.36, 16.4)	4.15 (1.18, 14.53)
Type 1 DM, n (%)	21 (4.0%)	21 (4.2%)	0 (0.0)	1.00	n/a	n/a
Previous MI/stroke, n (%)	112 (21.4%)	103 (20.4%)	9 (47.4%)	**0.009**	2.84 (1.1, 7.24)	1.54 (0.58, 4.10)
Previous known arrhythmia, n (%)	34 (6.5%)	29 (5.8%)	5 (26.3%)	**0.005**	5.84 (1.97, 17.3)	4.79 (1.52, 15.10)
Diabetic neuropathy or retinopathy, n (%)	66 (12.6%)	61 (12.1%)	5 (26.3%)	0.078	2.59 (0.90, 7.44)	1.99 (0.67, 5.90)
COPD, n (%)	26 (5.0%)	24 (4.8%)	2 (10.5%)	0.089	2.36 (0.51, 10.80)	1.85 (0.39, 8.82)
CHF, n (%)	17 (3.2)	14 (2.8%)	3 (15.8%)	**0.004**	6.58 (1.72, 25.18)	5.22 (1.26, 21.64)
BMI ≥ 30, n (%)	493 (94.1%)	474 (93.9%)	19 (100%)	0.616	n/a	n/a
Current smoker? n (%)	78 (14.9%)	75 (14.9%)	3 (15.8%)	0.999	1.08 (0.31, 3.78)	1.41 (0.38, 5.18)
Former smoker? n (%)	164 (31.3%)	155 (30.7%)	9 (47.4%)	0.135	2.03 (0.81, 5.10)	1.36 (0.53, 3.51)
Hypertensive or taking antihypertensive medication, n (%)	444 (84.7%)	426 (84.4%)	18 (94.7%)	0.334	3.34 (0.44, 25.36)	1.75 (0.22, 13.79)
Dyslipidemia or lipid- lowering medication, n (%)	445 (84.9%)	428 (84.8%)	17 (89.5%)	0.752	1.53 (0.35, 6.75)	1.17 (0.26, 5.32)
Chest pain recorded on testing? n (%)	22 (4.2%)	19 (3.8%)	3 (15.8%)	**0.040**	4.80 (1.29, 17.87)	4.79 (1.19, 19.29)

Odds ratio for BMI ≥ 30 is n/a, owing to all subjects with events having BMIs > 30. Bold values represent statistically significant values.

BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease.

* *P* value for comparison between CV outcome vs no CV outcome.

† Adjusted for age and sex.

outcomes; this should serve as a reminder to ask patients about symptoms and for exercise staff to educate patients to report potential ischemic symptoms within the context of exercise programming and progression.

In people with diabetes, traditional CVD risk factors—such as older age, sedentary lifestyle, hypertension, hyperlipidemia, and obesity—are very common. However, our findings suggest that presence of these risk factors did not discriminate between those with subsequent CV events and those without. Also, stress testing did not appear to reduce the number of CV events. In fact, 6 of the CV events within 1 year occurred in patients who had undergone stress tests and been cleared for the exercise program.

Although older studies reported much higher cardiac event rates,[2] the low rate of CV events found in our study is consistent with more recent trials in patients with type 2 diabetes.[18,28] In these recent trials, the low rates of cardiac events were unexpected, but not necessarily surprising, as rates of CV events in people with diabetes have declined markedly in recent years.[29] Over the last decade, application of optimal medical treatment, including aggressive pharmacologic risk-factor modification, has been the recommended approach. This is evident in the current study, with ~ 85% of the patients referred for stress testing reporting use of antihypertensive and/or lipid-lowering medication. Within the context of pre-exercise screening, it may be a more effective and efficient strategy to ensure that people with diabetes are receiving optimal medical therapy rather than recommend routine stress testing before engaging in a moderate exercise program.

Although this is, to our knowledge, the first population-based study to compare CV event rates in patients referred or not referred for pre-exercise stress testing in people with diabetes, there are several caveats to our findings. This was a retrospective cohort study rather than a randomized trial, which limits our ability to draw causal inferences. However, the nature of our unselected/nonvolunteer cohort may not be subject to the biases that can accompany patients recruited into randomized trials. The small number of CV outcomes is a key finding of the study but also limits the conclusions that can be drawn. The policy of the exercise program was not to refer asymptomatic patients of low physical function (ie, incapable of achieving at least 3 metabolic equivalents) for exercise stress testing before the exercise program, which may have led to underrepresentation of patients with lower functional capacities who would likely have been at greater risk of CVD. These patients participated in an exercise class more targeted to improving mobility and prevention of falls rather than aerobic exercise. Furthermore, as many patients had self-selected to participate in the exercise program, our study population was likely healthier than the overall clinical diabetic population. The relatively short follow-up period may also limit the generalizability of the findings. Most data collected were from clinical and administrative databases not created for research purposes. The lack of clinical details beyond age and sex for the patients not referred for screening does not allow for a detailed comparison to those referred for testing or the adjustment for clinical covariates. However, it should be noted that chart data were abstracted on all those who experienced CV outcomes. In fact, the review of more than 500 clinic charts allowed for a rich dataset on presence of comorbidities and insights into the clinical decisions and end outcomes of the referral to screening clinics.

Conclusions

Although stress testing can be useful in exercise prescription and assessing long-term prognosis,[30] concerns with costs, barriers, follow-up with expensive/invasive tests, and potential low yield suggest that it may be impractical to use stress testing to screen for CAD in all or most asymptomatic patients with diabetes who want to begin exercise programs. Based on our findings, we suggest that recommendations for stress testing before beginning an exercise program for all patients with diabetes are too broad. We propose that pre-exercise stress testing be reserved for patients with diabetes who have symptoms suggesting ischemia or have known CAD, arrhythmias, CHF, and/or microvascular complications and perhaps those planning very vigourous exercise (such as racing, long-distance running or high-intensity interval training). Minimizing the need for pre-exercise stress testing through better risk stratification will help manage costs, reduce unnecessary follow-up testing, and reduce barriers to structured exercise programming, ideally resulting in increased participation in exercise by people with diabetes.

Author's Note

This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta nor, Alberta Health or Alberta Health Services express any opinion in relation to this study.

Acknowledgements

The authors would like to thank members of the Alberta Provincial Project for Outcome Assessment in Coronary Heart disease (APPROACH) steering committee and staff as well as the staff at the screening clinics (C-era, Mayfair Diagnostics, and TotalCardiology) and staff at the Alberta Healthy Living Program (formerly the Living Well with a Chronic Condition Program), who helped make this study possible.

Funding Sources

Dr Armstrong was supported by a Doctoral Studentship Award, and Dr Sigal was supported by a Health Senior Scholar Award, both from Alberta Innovates-Health Solutions, Alberta, Canada.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006;368:29-36.

2. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.

3. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care 2000;23:962-8.

4. Seshasai SR, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829-41.

5. Church TS, Cheng YJ, Earnest CP, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. Diabetes Care 2004;27:83-8.

6. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med 2005;165:2114-20.

7. Sluik D, Buijsse B, Muckelbauer R, et al. Physical activity and mortality in individuals with diabetes mellitus: a prospective study and meta-analysis. Arch Intern Med 2012;6:1-11.

8. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of moderate to vigorous physical activity on all-cause mortality in middle-aged and older australians. JAMA Intern Med 2015;175:970-7.

9. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. JAMA 2002;288:1994-2000.

10. Albert CM, Mittleman MA, Chae CU, Lee I-M, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. N Engl J Med 2000;343:1355-61.

11. Thompson PD, Franklin BA, Balady GJ, et al. Exercise and acute cardiovascular events: placing the risks into perspective: a scientific statement from the American Heart Association. Circulation 2007;115:2358-68.

12. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2017: ch 2 and 10.

13. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128:873-934.

14. Riddell MC, Burr J. Evidence-based risk assessment and recommendations for physical activity clearance: diabetes mellitus and related comorbidities. Appl Physiol Nutr Metab 2011;36:S154-89.

15. Arena R, Myers J, Guazzi M. The future of aerobic exercise testing in clinical practice: is it the ultimate vital sign? Future Cardiol 2010;6:325-42.

16. Franklin BA. Preventing exercise-related cardiovascular events: is a medical examination more urgent for physical activity or inactivity? Circulation 2014;129:1081-4.

17. Muhlestein JB, Lappe DL, Lima JA, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA 2014;312:2234-43.

18. Young LH, Wackers FJT, Chyun DA, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study. JAMA 2009;301:1547-55.

19. Lievre M, Moulin P, Thivolet C, et al. Detection of silent myocardial ischemia in asymptomatic patients with diabetes: results of a randomized trial and meta-analysis. Trials 2011;12:23.

20. Standards of Medical Care in Diabetes—2017: summary of revisions. Diabetes Care 2017;40:S4-5.

21. Poirier P, Bertrand OF, Leipsic J, Mancini GBJ, Raggi P, Roussin A. Screening for the presence of cardiovascular disease. Can J Diabetes 2018;42(suppl 1):S170-7.

22. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care 2010;33:e147-67.

23. Bruce RA. Exercise testing of patients with coronary heart disease: principles and normal standards for evaluation. Ann Clin Res 1971;3:323-32.

24. McInnis KJ, Balady GJ. Comparison of submaximal exercise responses using the Bruce vs modified Bruce protocols. Med Sci Sport Exer 1994;26:103-7.

25. Ghali WA, Knudtson ML. Overview of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease. Can J Cardiol 2000;16:1225-30.

26. Canadian Institute of Health Information. Canadian coding standards for ICD-10-CA and CCI for 2006. Ottawa, Canada: Canadian Institute for Health Information; 2006.

27. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. Am Heart J 2002;144:290-6.

28. Look AHEAD-Research-group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-54.

29. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990—2010. N Engl J Med 2014;370:1514-23.

30. Ashley EA, Myers J, Froelicher V. Exercise testing in clinical medicine. Lancet 2000;356:1592-7.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.11.007.